IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Himmelsbach, Frank *et al.*	Examiner: Truong, Tamthom Ngo
Serial No.:	10/023,099	Group Art Unit: 1624
Filed:	December 17, 2001	Docket: 5/1310
Confirmation No.	2352	
For:	QUINAZOLINE DERIVATIVES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM	

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF DR. FRANK HIMMELSBACH UNDER 37 C.F.R. § 1.132

Sir:

I, Frank Himmelsbach solemnly state and declare as follows:

1. My technical background is as follows:

   I am a trained chemist having received a doctorate (Dr. rer. nat.) in chemistry from the University of Konstanz, Germany in 1984 .

   I did a postdoctoral study at the Imperial College London from September 1984 to December 1984. I joined the Department of Chemistry of Dr. Karl Thomae GmbH, Biberach/Riss, Germany in 1985 as Head of Laboratory, and I presently hold the position of Group Leader in the Department of Chemistry Research of Boehringer Ingelheim Pharma GmbH & Co. KG (formerly named Dr. Karl Thomae GmbH), Biberach/Riss, Germany.

   I am a member of the "Gesellschaft Deutscher Chemiker" (Society of German Chemists).

2. I am a co-inventor of the above-identified patent application, and I am familiar with the subject matter of the above-identified patent application.

3. I am familiar with the U.S. P.T.O. Office Action dated October 10, 2003 in the above-identified application.

4. Under my responsibility and control as Group Leader in the Department of Chemistry Research of Boehringer Ingelheim, I supervised the screening and evaluation of compounds under the research division's program directed to the development of compounds that target the family of receptor tyrosine kinases.

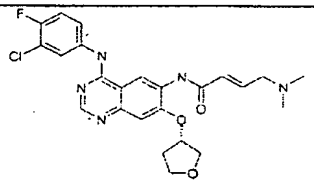
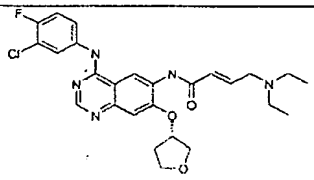
5. In order to demonstrate activity against the family of receptor tyrosine kinases for the compounds of the present invention, inhibition of epidermal growth factor receptor (EGF-R) kinase and HER2 tyrosine kinase was performed according to the assay described on pages 18 to 19 of the above-identified application using the cytoplasmic tyrosine kinase domain (methionine 664 to alanine 1186, based on the sequence published in Nature 309 (1984), 418) of EGF-R expressed in Sf9 insect cells as a GST fusion protein using the Baculovirus expression system. Testing on HER2 tyrosine kinase was performed accordingly, using the cytoplasmic tyrosine kinase domain (lysine-676-methionine to valine 1255, based on the sequence published in Science 230 (1985), 132) of HER2 cloned into Baculovirus and expressed in Sf9 insect cells.

The results shown in the following table demonstrate that the compounds of the invention inhibit both EGF-R kinase and HER2 tyrosine kinase.

Compound (Example No.)	Inhibition of EGF-Receptor kinase IC50 [nM]	Inhibition of HER2 tyrosine kinase IC50 [nM]
1	0.7	45
1(2)	0.6	21
1(3)	4.0	572
1(5)	3.0	533
1(10)	0.5	14
1(22)	1.0	68
1(32)	0.3	40
1(33)	0.5	18
1(34)	0.4	8

6. In order to demonstrate the unexpectedly improved inhibition of kinases of the tyrosine kinase family by the compounds of the present invention, a compound of the present invention (Example 1(10) of the present application) and a structurally similar compound (Example 3(30) of U.S. Patent Publication No. 2002/0169180) were screened in the EGF-R kinase and HER2 tyrosine kinase assays described on pages 18 to 19 of the above-identified application and in paragraph 5 above. The compounds differ only slightly in the R_b group. The R_b group of the compound of the invention is a dimethylamino group whereas the R_b group of the structurally related compound is a diethylamino group.

The results obtained are shown in the following table:

Compound (Example No.)	Structure	Inhibition of EGF-Receptor kinase IC_{50} [nM]	Inhibition of HER2 tyrosine kinase IC_{50} [nM]
1(10)		0.5	14
3(30)		5	126

7. From the above comparative experiments and results, I conclude that the compounds according to the invention of the above-identified patent application are much more active with regard to tyrosine kinase inhibition than other structurally similar compounds. Furthermore, I conclude that such activity results would have been both surprising and unexpected to one of ordinary skill in the art of the subject matter of the invention.

The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: April 8, 2004 Signature: F. Himmelsbach

Frank Himmelsbach